IMPACT

CHANGING THE OUTCOMES OF BATTEN DISEASE

BATCure

This project is funded by the European Union

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Due to the rarity of the neurodegenerative conditions known collectively as Batten disease, not much is known about them from a general clinical or public perspective. ***BATCure*** *aims to address part of this problem by developing therapeutics for three types of the disease*

Batten disease was first described in Sweden in 1826 and in the UK in 1903, but the first genes involved in its onset were only identified in 1995. They were the first of many, because Batten disease is not a single condition, but rather a group of diseases, with over 400 mutations in 13 different genes currently known to be involved in the various forms. While relatively speaking Batten disease is rare, affecting approximately 14,000 people worldwide with around 1,400 new cases every year, it is a particularly tragic affliction as the majority of those affected are children. Those with the disease will experience devastating symptoms such as visual impairment and blindness, severe epileptic seizures that are difficult to control, involuntary muscle spasms, speech loss, swallowing difficulties and the deterioration of motor skills. Ultimately, the disease is fatal, and there are no established treatments.

BATCure is a project that has the ambitious and inspiring objective of developing effective treatments for patients with three types of Batten disease. It began in January 2016 and will run for three years, having been granted nearly 6 million euros of European Union funding. The project is coordinated by Professor Sara Mole of University College London (UCL), UK, who has been working on Batten disease for more than two decades, and has already made progress towards the development of new therapies. The project also has a large consortium of members selected from across Europe to provide the relevant expertise and resources that will be required to address each of the key objectives of the project. The lack of established treatments for Batten disease means the consortium has a big job to do. As such there are several different aspects to their work, making collaboration absolutely crucial, and Mole feels that things are going smoothly so far. 'Despite about half being new to Batten disease and to each other, I'm pleased to say that all partners have been working together incredibly well,' she enthuses.

A PHASED APPROACH

While there are many diseases under the umbrella term 'Batten disease', BATCure focuses on three genetically distinct sub-types, which affect over 50 per cent of children and young adults living with the disease across Europe. The team is taking a multifaceted approach to the project in order to maximise their chances of success. 'The challenges of reaching therapies for Batten disease are such that it requires tackling on multiple fronts,' explains Mole. The team hopes to develop new gene therapies, for example, but they are also looking at whether it is possible to repurpose existing drugs. This may aid the design of new compounds, and ultimately achieve the objective of finding effective treatments.

The work of BATCure is divided into three phases: pre-discovery, discovery and pre-clinical. There are a total of eight experimental work packages, each led by an expert in that specific area and supported by other partners, aiming to address a single objective that forms the wider project. The first three packages focus on developing new models, identifying therapeutic target pathways and establishing new monitoring and diagnostic techniques. Moving beyond this, the team will look at the wider natural history of the brain, identify new compound leads and determine therapeutic potential using zebrafish. As the work progresses, the team will assess gene therapy for the brain, eye and other organs, and also deliver a new small molecule therapy to mice.

> *'The challenges of reaching therapies for Batten disease are such that it requires tackling on multiple fronts'*

BATCure Consortium at UCL

Alongside the research side of the project are two supporting work packages. These include the management of the project and the involvement of patient organisations. Many partners contribute to multiple work packages and all the work packages rely on input from other partners, so collaboration and sharing of information and data are built into the project.

THE PATH TO DISCOVERY

As the project has been running since January 2016, there will soon be an evaluation of the preliminary results to assess what is to be expected over the rest of its term. While this has not yet taken place, the group has already made findings that will inform their work. One example of this is in the treatment applied in mice. Significantly, they found that in one of the types under study, to treat the loss of photoreceptor cells – involved in the onset of blindness – it is necessary to target cells in the middle layer of the retina rather than the photoreceptor cells themselves. This was an unexpected result and is unusual in terms of experience with gene therapy for other genetic causes of blindness.
Looking ahead to the end of the project, it is hoped that BATCure will be continued and that funding will be secured for clinical trials to capitalise on the work that has already been undertaken. The team also wants similar work to be applied to other types of Batten disease, should funding be secured. Despite having 14 consortium members spread across seven different countries, the BATCure team is working efficiently together towards its goals, and they all have long term ambitions regarding this disease.

BREAKING NEW GROUND

Batten disease is particularly distressing due to its degenerative nature. As a child with the disease gets older, they slowly lose all of their abilities and become completely dependent on families and carers. Existing treatment is only palliative, and can do little more than address certain symptoms. The disease is also very rare, and this presents a number of further challenges for those affected and their families. It is often local physicians who are the first point of call for patients, yet most will never have seen a case of Batten disease. This may extend the amount of time before a patient is given their diagnosis. Parents may have to give up work in order to provide round-the-clock care, and social support may be required to try to lessen the emotional, physical and financial burden.

Furthermore, rare diseases like Batten disease are always up against the challenge of funding. There is not as much money available to support research into them, meaning progress is often slow. While this is understandable to a certain extent, as obviously rare diseases by their very nature affect fewer people, it may be an oversight. Such diseases can often provide key insights into fundamental biology, and therefore funding and research support for them can have a broad impact that goes beyond a specific disease.

Given the nature of the disease and the total lack of treatments, BATCure is offering a rare glimpse of hope for those affected and their families. The collaborative working and science that is behind the project offers huge potential that is already on its way to being realised.

Project Insights

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PARTNERS
University College London (UCL) • Acureomics • Latvijas Organiskas Sintezes Instituts • Cardiff University • Fondazione Telethon • Universitaetsklinikum Hamburg-Eppendorf • Pronexus • Manchester Metropolitan University • Royal Veterinary College • Universidad Salamanca • Orphazyme • Kings College London • Acondicionamiento Tarrasense Associacion (LEITAT) • Batten Disease Family Association

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PROJECT LEADER BIO
Professor Sara Mole is a Great Ormond Street Hospital Children's Charity Professor at University College London. Her main research interest is the neuronal ceroid lipofuscinoses or Batten disease, a group of inherited neurodegenerative diseases that affect lysosome homeostasis.

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Impact Objectives

- Create new models, tools and technologies for developing and testing therapies for Batten disease
- Triage new compound treatments
- Provide a novel mechanism to fully involve patients and their families, and prepare all stakeholders for clinical trials

Coordinating a cure

Batten disease is a group of neurodegenerative diseases that are life-limiting, and are made all the more tragic because they mainly affect children. **Professor Sara Mole** *at* ***University College London*** *is coordinating* ***BATCure****, a project that aims to tackle the disease*

Can you begin by explaining what Batten disease is, and what its effects are?

Batten disease is a broad classification for more than a dozen separate monogenic recessive disorders, also known as the neuronal ceroid lipofuscinoses, which share common clinical features. These features are caused by neuron loss within the central nervous system and the storage of autofluorescent material in most cell types, which has a typical pattern in electron microscopy. Batten disease mainly affects children, who suffer progressive dementia, motor decline, visual failure and epilepsy. The disease course leads to a long period of complete dependence on others, and is life-limiting. Existing palliative treatment can help, but cannot eliminate the burden of seizures and the progressively worsening effects on the whole body due to decreasing central nervous system influence and control.

What are the key objectives of BATCure?

The goal of BATCure is to develop effective treatments for patients living with a group of rare lysosomal diseases known as Batten disease. It will provide concerted, focused and synergistic action by experts committed to working together towards this common goal.

How will the consortium behind BATCure achieve this goal?

BATCure will focus on therapeutic development for three types of Batten disease, including the most common type – CLN3 disease – which affect at least half of all cases. Therapeutic development has been neglected for these types, with no clinical trials directly addressing the disease in existence when we began this project. Therapy for diseases caused by dysfunctional intracellular transmembrane proteins requires a trans-disciplinary and therefore coordinated approach, and new and emerging technologies now allow this goal to be addressed. Finally, it's important to note that our strategic approach and the new therapies that are devised may benefit other diseases, both rare and more common.

We see drug and gene-based approaches as the most likely to be beneficial for those affected by CLN3 disease, as well as other types of Batten disease such as CLN6 and CLN7 diseases. We will apply a novel strategic approach to drug discovery, which has significant advantages over drug discovery programmes based on mode-of-action approaches, and which is also integrated with gene therapy development. Our innovative approach adapts and modifies the best aspects of the function-based and physiology-based approaches previously described to provide biological efficacy of compounds, and is tailored to meet the specific needs of Batten disease. There is the required expertise within the BATCure consortium for all planned activities and integration of disciplines at all stages.

What inspired this project and how did you become the coordinator for it?

This is an EU collaborative research project, which is an ideal platform for collaborative work. I watched out for a call that was relevant to this type of work and on the day one was announced, I invited a small group in London to meet and begin to plan a collaborative project. I then invited the required experts from across Europe to engage with the project.